

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)



Applicant's or agent's file reference 61.78607/001	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/GB 03/02942	International filing date (day/month/year) 07.07.2003	Priority date (day/month/year) 10.07.2002
International Patent Classification (IPC) or both national classification and IPC C12N9/74		
Applicant NATIONAL BLOOD AUTHORITY et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of sheets.

- This report contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 28.01.2004	Date of completion of this report 27.07.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Vix, O Telephone No. +49 89 2399-7326 

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EXAMINATION REPORT**

International application No. **PCT/GB 03/02942**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-32 as originally filed

Claims, Numbers

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-8
	No: Claims	9-13
Inventive step (IS)	Yes: Claims	1-8
	No: Claims	9-13
Industrial applicability (IA)	Yes: Claims	1-13
	No: Claims	

2. Citations and explanations

see separate sheet

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Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1: EP-A-0 543 178 (BEHRINGWERKE AG) 26 May 1993 (1993-05-26)
- D2: EP-A-0 439 156 (WARNER LAMBERT POTTERY ROAD LI) 31 July 1991
- D3: EP-A-1 136 084 (AVENTIS BEHRING GMBH) 26 September 2001
- D4: WO 00/71153 A (BIO PROD & BIO ENG AG ;EIBL JOHANN (AT)) 30 November 2000 (2000-11-30)
- D5: EP-A-0 565 511 (IMMUNO AG) 13 October 1993 (1993-10-13)
- D6: GOLDSACK NEIL ET AL: "Molecules in focus thrombin" International. J. of Biochem and Cell Biol., vol. 30, no. 6, June 1998, pgs 641-646

Additional document:

D7: EP1161958

1. Novelty (Art. 33(2) PCT)

- 1.1** The application relates to a method for the preparation of virus-inactivated thrombin comprising solvent-detergent virus inactivation of a solution comprising prothrombin and factor X, loading the virus inactivated prothrombin and factor X onto an anion exchange medium, washing the medium to remove the reagents used for the solvent-detergent virus inactivation, and activating the prothrombin on the medium to form thrombin by the addition of metal ions, preferably calcium ions. The thrombin is then preferably selectively eluted from the anion exchange medium.

None of the available prior art specifically discloses this combination of steps in a method for producing a virus-inactivated thrombin. Thus, in view of the available prior art, the claimed subject-matter 1-8 appears to be new. Consequently, claims 1-8 do meet the requirements of Article 33(2) PCT.

- 1.2** The applicant's attention is drawn to the fact that product by process claims as defined in claims 9-11 and 12-13 will not be admissible in the European regional phase. Such claims are admissible only if the product (thrombin in the present case) by itself fulfil the requirements for patentability and there is no other

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information available in the application which could enable the applicant to define the product satisfactorily by reference to its composition, structure or some other testable parameter. Thrombin is a well known and studied protein which can be prepared using various methods as disclosed in the prior art D1-D4. The applicant's attention is drawn to the fact that a product is not rendered novel merely by the fact that it is purified by means of a new process.

At present, all applications such as D1-D4 disclosing thrombin (and its obtention/preparation) or pharmaceutical composition/kit comprising thrombin are prejudicial for the novelty and inventivity of claims 9-13 under Art 33(2)/(3) PCT.

2. Inventive step (Art. 33(3) PCT)

The application relates to a method for the preparation of virus-inactivated thrombin comprising solvent-detergent virus inactivation of a solution comprising prothrombin and factor X.

The available prior art D1-D3 relate to the preparation of thrombin free of viral contaminant based on various method/process.

D1 relates to a purified thrombin preparation free from viral contamination. The method comprises treating a solution of prothrombin complex, which has been purified on an ion exchanger and subjected to virus inactivation, with a soluble salt containing an anion.

Another example is D2 which discloses a process for the production of a liquid thrombin preparation which comprises reacting each unit of prothrombin with less than 50% of the conventional thromboplastin input in the presence of calcium, contacting the resultant thrombin with a phosphate buffer, and diluting and filtering the suspension. The filtrate is then applied sequentially to an anion-exchange agarose column and a cation-exchange agarose column and the thrombin fraction is step-wise eluted from the latter column with phosphate buffered saline.

Based on the teaching of the prior art such as D1, the technical problem to be solved could be seen as the provision of an alternative method for producing a virus inactivated thrombin preparation.

As seen from D1 or D3, protein preparation can be treated using different virus inactivation processes. Other methods are known to the skilled person in the art

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such as solvent-detergent virus inactivation steps. For example, D7 discloses a method for inactivating viruses in biological liquid solution which comprises contacting the biological liquid solution with solvent detergent mixture. The solvent detergent mixture at a predetermined concentration and conditions is able to inactivate lipid-coated viruses. The solvent-detergent mixture is removed by passing the liquid solution on a chromatographic packing.

Thus, in the light of D1 and D7, the present subject-matter of claims 1-8 could be seen as the combination of a known solvent-detergent technique and anion-exchange chromatography purification steps applied to thrombin. However, D1 does not suggest that activation of prothrombin complex to form thrombin could occur while bound to an anion exchange medium, nor does it suggest to combine this technique with a solvent-detergent virus inactivation treatment.

As the claimed method allows the efficient preparation of virus-safe thrombin without any addition of thrombin or thromboplastin for activation (like in D1 or D2), using solvent-detergent treated prothrombin bound to an anion exchange medium and use of metal ions to activate the prothrombin to form thrombin, said method is considered to achieve a surprising technical effect over the available prior art. Thus, the presence of an inventive step within the subject-matter of claims 1-8 is acknowledged. Consequently, said claims do meet the requirements of Article 33(3) PCT.